

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re United States Patent Application of:	}	Docket No.:	4258-118	
Applicant(s):	FABRE, Myriam, et al	}	Examiner:	Deborah K. Ware
Application No.:	10/563,033	}	Art Unit:	1651
Date Filed:	December 30, 2005	}	Conf. No.:	6057
Title:	METHOD OF STORING AND/OR TRANSPORTING IN VITRO CELL CULTURES	}	Customer No.:	23448

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**DECLARATION OF Francesc Mitjans UNDER 37 CFR §1.132  
IN U.S. PATENT APPLICATION NO. 10/563,033**

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Mail Stop AF  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Francesc Mitjans hereby declares:

1. THAT I am an independent scientist of the subject matter disclosed and elected in United States Patent Application No. 10/563,033 filed in the U.S. Patent and Trademark Office on December 30, 2005 in the names of Myriam Fabre, Sonia Gonzalez Menoyo, Mariama Lopez Matas and Roser Pagan I Esquius, and entitled, "METHOD OF STORING AND/OR TRANSPORTING IN VITRO CELL CULTURES," hereafter referred to as the "Application."
  
2. THAT the Application relates, in general, to obtaining a singular method of storing and/or transporting in vitro cell cultures. The claims being examined specifically relate to a novel methodology for storing or transporting two-dimensional cell cultures preserving their functional properties; Conclusions stated are as follow:

- The specific and intricate parameter combination (gelatine concentration, solidifying and storing temperature, solidifying and storing time) of the claimed methodology, could not be obtained by chance by performing easy laboratory assays.
- The cell model used in the claimed methodology is also innovative, due to the fact that it is an *in vitro* and polarized one, meaning that it is necessary to previously immobilize these cells on an asymmetric support enabling the induction of differentiation and polarization afterwards prior to coating with gelatine.

Some of the novelty issues of this methodology rely on the fact that this kind of models are of such structural complexity, that it is almost impossible for the skilled person to maintain their functional properties intact during a certain time frame in order to perform related cellular assays.

- The medium supplemented with gelatin directly coats the whole cellular model, leaving no cells in direct air contact. There is nothing in the prior art similar to this fact because of the usual death of cells, as soon as their whole surface is in contact with this kind of medium. The uniqueness of the claimed methodology solves this last cellular death problem.
- The information contained in previous scientific publications, would lead away a skilled person from completely coating with gelatine any cell culture, since this could seriously affect the cell functionality.

As a below-named declarant, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements, and the like, so made are punishable by fine or imprisonment, or both, under Section 1001 or Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Francesc Mijangs

Date 09-May-2011

**EUROPEAN  
CURRICULUM VITAE  
FORMAT**



**PERSONAL INFORMATION**

Name **FRANCESC MITJANS PRAT**  
Address **C/BALDIRI REIXACH, 15-21, 08028 BARCELONA**  
Telephone **934020417**  
Fax  
E-mail **fmitjans@leitat.org**  
  
Nationality **Spanish**  
Date of birth **29/01/1965**

**WORK EXPERIENCE**

- Dates **March 2008 – today**  
Name and address of employer **Leitat Technological Center. Biomed Division. Parc Científic de Barcelona. C/Baldíri Reixach, 15-21, 08028 Barcelona**  
Type of business or sector **Biomed/Pharmaceutical I+D**  
Occupation or position held **Biomed Division Director**  
Main activities and responsibilities **Pre-clinical research - oncology**
  
- Dates (from – to) **January 2005 – January 2008**  
Name and address of employer **Laboratorio de Bioinvestigación (LBI). Merck Farma y Química, S.A.**  
Type of business or sector **Pharmaceutical Industry**  
Occupation or position held **Department Head (Group Leader)**  
Main activities and responsibilities **Director of several research projects at pre-clinical and clinical level.  
Management of a 6 staff team developing technical and scientific tasks.  
Responsible of the pre-clinic area in clinical projects.  
Development of pre-clinical projects.  
Participation in the achievement of phase I clinical trials for new anti-tumor drugs.  
Identification and management of national and international collaborations.**
  
- Dates (from – to) **January 2000 – January 2005**  
Name and address of employer **Laboratorio de Bioinvestigación (LBI). Merck Farma y Química, S.A.**  
Type of business or sector **Pharmaceutical Industry**  
Occupation or position held **Laboratory Head**  
Main activities and responsibilities **Leader of several pre-clinical research projects.  
Management of a 10 staff team developing technical and scientific tasks.  
Responsible of the development of pre-clinical projects.  
Leadership in the progression of projects from the pre-clinical phase up to the clinical phase.  
Development of new oncologic drugs.  
Identification and management of national and international collaborations..**
  
- Dates (from – to) **February 1991 – January 2000**

- Name and address of employer
  - Type of business or sector
  - Occupation or position held
- Main activities and responsibilities
 

Laboratorio de Bioinvestigación (LBI). Merck Farma y Química, S.A.  
 Pharmaceutical Industry  
 Project Leader

Participation in several pre-clinical research projects.  
 Management of a 4 staff team developing technical and scientific tasks.  
 Responsible of the development of pre-clinical projects.  
 Co-leadership in the progression of projects from the pre-clinical phase up to the clinical phase.  
 Development of new oncologic drugs.  
 Identification and management of national and international collaborations.  
 Identification and characterization of new pharmacological targets in apoptotic processes.  
 Study of the expression and modulation of new epitopes related to the metastatic spread of tumor cells and tumor angiogenesis.  
 Immunogenicity analysis of tumor related antigens.

## EDUCATION AND TRAINING

<ul style="list-style-type: none"> <li>• Dates</li> <li>• Name and type of organisation providing education and training</li> <li>• Principal subjects/occupational skills covered</li> <li>• Title of qualification awarded</li> <li>• Level in national classification (if appropriate)</li> </ul>	<p>1998 – 2001        DOCTORAL THESIS (PHD) University of Barcelona, Barcelona, Spain        "Effect of avb3 integrin antagonists in melanoma progression and tumor angiogenesis"</p> <p>Doctor (PhD)        Excellent Cum Laude unanimously.        Award winner of the University of Barcelona Doctor Senate Prize.</p>
<ul style="list-style-type: none"> <li>• Dates</li> <li>• Name and type of organisation providing education and training</li> <li>• Title of qualification awarded</li> </ul>	<p>1989        Biologist. University of Barcelona, Barcelona, Spain</p>
	<p><b>BACHELOR DEGREE</b></p>
<ul style="list-style-type: none"> <li>• Dates</li> <li>• Name and type of organisation providing education and training</li> <li>• Principal subjects/occupational skills covered</li> </ul>	<p>2007        Mondial Research Group LTD. Brussels.        "ADME, PK/TK, and drug metabolism in drug discovery and development".</p>
<ul style="list-style-type: none"> <li>• Dates</li> <li>• Name and type of organisation providing education and training</li> <li>• Principal subjects/occupational skills covered</li> </ul>	<p>2007        Universitat Autònoma de Barcelona &amp; Quality Assurance Unit from LBI (Merck Farma y Química, S.A.        "Introduction to the Good Laboratory Practices (GLP)".</p>

## ADDITIONAL INFORMATION

## PATENTS

- Hernández JL, Adan J, Martínez JM, Masa M, Messeguer R, Mitjans F, Coll A, Hervas R, Calvis C, Dakhel S. Antibodies for cancer therapeutic and diagnostic use. EP11382010.4. Leitat Technological Center.
- Mitjans F, Adan J, Calvis C, Lavilla R, Miguel M, Albericio F, Ruiz J. RGD amino acid cyclic peptides based on thiazoles or oxazoles as selective antagonists of αvβ3 integrin. EP10388229.0. Leitat Technological Center.
- Hernández JL, Adan J, Martínez JM, Masa M, Messeguer R, Mitjans F, Coll A, Hervas R, Calvis C, Dakhel S. Antibodies for therapeutic use. P25126EP00. Leitat Technological Center.
- Goodman S, Hahn D, Mitjans F, Adan J, Lo K-M. Engineered anti-alpha v-integrin hybrid antibodies. International Patent nº WO 2009/010290 A2.
- Hölzemann G, Crassier H, Ackermann KA, Stähle W, Jonczyk A, Rautenberg W, Mitjans F, Rosell-Vives E, Adan J, Soler M. Aminobenzimidazole derivatives. United States Patent 20070021456. International Patent nº WO 2005/019216 A1.
- Hölzemann G, Crassier H, Ackermann KA, Stähle W, Jonczyk A, Rautenberg W, Mitjans F, Rosell-Vives E, Adan J, Soler M. Pyridopyrimidinones. United States Patent 20070099910. International Patent nº WO 2005/047283 A1.
- Hölzemann G, Ackermann KA, Stähle W, Jonczyk A, Rautenberg W, Mitjans F, Rosell-Vives E, Adan J, Soler M. Urea derivatives. International Patent nº WO 2005/019192 A1.
- Hölzemann G, Crassier H, Jonczyk A, Stähle W, Sutter A, Rautenberg W, Mitjans F, Rosell-Vives E, Adan J, Soler M. Imidazol derivatives. International Patent nº WO 2005/097755 A2.
- Goodman S, Dieffenbach B, Mitjans F, Carceller A, Rosell E. Use of the antibody 271.14D9.F8 (DSM ACC2331) to inhibit *in vitro* αsphavbeta6- integrin attachment to fibronectin. International Patent nº WO 1999/037683
- Mitjans F, Goodman SL, Carceller A, Dieffenbach B, Rosell E. (1998). Adhesion receptor blocker for alpha v integrins. International Patent nº: EP 98101108.3
- Mitjans F, Adan J, Piulats J, Goodman SL, Rosell E, Hahn D. (1995). Anti-αvβ3 integrin monoclonal antibody. International Patent nº: 95 119 233.5
- Kettleborough CA, Bending M, Gussow D, Adan J, Mitjans F, Rosell E, Blasco F, Piulats J. (1995). Anti-EGFR single chain Fvs and anti-EGFR antibodies. International Patent nº WO 95/25167

## ORAL COMMUNICATIONS AS INVITED SPEAKER

- Role of the anti-angiogenesis therapies. XIV Congress of the Catalan Society of Gastroenterology Advances in Malignant Melanoma. Roses, Spain (2005).
- Tumor angiogenesis: Key role of integrins. World Conference on Magic Bullets. "Celebrating Paul Ehrlich's 150<sup>th</sup> birthday". Nürnberg, Germany (2004).
- αv-integrins and tumor angiogenesis. Angiogenesis, SMI Pharmaceutical Conferences. London, UK (2003).
- Anti-angiogenic therapy using integrin antagonists. Emerging BioTherapy of Cancer. 17th Meeting of the European Association for Cancer Research (EACR). Granada, Spain (2002).
- Role of αv-integrins in tumor angiogenesis. Angiogenesis & Anti-Angiogenesis Therapeutics, SMI Pharmaceutical Conferences. London, UK (2002).
- Alphav beta3, a pivotal integrin. Research Based Oncology, SMI Pharmaceutical Conferences. London, UK (2001).

## PUBLICATIONS

- Marchán S, Pérez-Torras S, Vidal A, Adan J, Mitjans F, Carbó N, Mazo A. Dual effects of  $\beta 3$  integrin subunit expression on human pancreatic cancer models. *Anal Cell Pathol (Amst)*. 2010 Sep 8
- Cupido T, Spengler J, Ruiz-Rodríguez J, Adan J, Mitjans F, Piulats J, Albericio F. Amide-to-ester substitution allows fine-tuning of the cyclopeptide conformational ensemble. *Angew Chem Int Ed Engl*. 2010 Apr;49(15):2732-7
- Piulats J, Mitjans F. "Angiogenic switch pathways" in *Principles of Molecular Oncology*, 2008 (3d Edition), p.p. 411-441. Springer Books.
- Eds: MH Bronchud, M Foote, G Giaccone, O Olopade, and P Workman
- F. Mitjans y J. Piulats. Implicaciones clínicas de la investigación básica. Angiogénesis: diana de nuevos tratamientos oncológicos. *Gastroenterología y Hepatología Continuada*. 2007. 6(1): 27-31.
- Bosch B, Clotet-Codina I, Blanco J, Pauls E, Coma G, Cedeno S, Mitjans F, Llano A, Bofill M, Clotet B, Piulats J, Este JA. Inhibition of human immunodeficiency virus type 1 infection in macrophages by an alpha-v integrin blocking antibody. *Antiviral Res*. 2006 Mar;69(3):173-80.
- Fernandez Y, Queralt J, Pavía X, Piéra C, Ramirez de Arellano I, Mitjans F, Messeguer R, Piulats J, Carrío I. Multitracer in vivo assessment of tumor models with 18F-fluorothymidine, 18F-FDG and N-ammonia PET in mice *Eur J Nucl Med Mol Imaging* 2006, 33 (supl II): S249
- Fernandez Y, Queralt J, Pavía X, Ramírez de Arellano I, Mitjans F, Piulats J, Carrío I. Visualización de la actividad proliferativa tumoral mediante 18Ffluorotimidina en glioma y melanoma en ratón *Rev Esp Med Nucl* 2006, 25 Supl I:19
- Enns A, Korb T, Schlueter K, Gassmann P, Spiegel HU, Senninger N, Mitjans F, Haier J. Alphavbeta5-integrins mediate early steps of metastasis formation. *Eur J Cancer*. 2005 May;41(7):1065-72.
- Alhaja E, Adan J, Pagan R, Mitjans F, Cascallo M, Rodriguez M, Noe V, Ciudad CJ, Mazo A, Vilaro S, Piulats J. Anti-migratory and anti-angiogenic effect of p16: a novel localization at membrane ruffles and lamellipodia in endothelial cells. *Angiogenesis*. 2004;7(4):323-33.
- Coma S, Noe V, Lavarino C, Adan J, Rivas M, Lopez-Matas M, Pagan R, Mitjans F, Vilaro S, Piulats J, Ciudad CJ. Use of siRNAs and antisense oligonucleotides against survivin RNA to inhibit steps leading to tumor angiogenesis. *Oligonucleotides*. 2004;14(2):100-13.
- Piulats J, Mitjans F. "Angiogenic switch pathways" in *Principles of Molecular Oncology*, 2004 (2nd Edition), p.p. 411-441
- Eds: Bronchud, Robinson, Peters. Humana Press. New York.
- Bessa X, Elizalde JI, Mitjans F, Pinol V, Miquel R, Panes J, Piulats J, Pique JM, Castells A. Leukocyte recruitment in colon cancer: role of cell adhesion molecules, nitric oxide, and transforming growth factor beta1. *Gastroenterology*. 2002 Apr;122(4):1122-32.
- Castel S, Pagan R, Mitjans F, Piulats J, Goodman S, Jonczyk A, Huber F, Vilaro S, Reina M. RGD peptides and monoclonal antibodies, antagonists of alpha(v)-integrin, enter the cells by independent endocytic pathways. *Lab Invest*. 2001 Dec;81(12):1615-26.
- Braña MF, Anorbe L, Tarrason G, Mitjans F, Piulats J. Synthesis and biological evaluation of novel bisindolylmaleimides that inhibit vascular endothelial cell proliferation. *Bioorg Med Chem Lett*. 2001 Oct 22;11(20):2701-3.
- Castel S, Pagan R, García R, Casaroli-Marano RP, Reina M, Mitjans F, Piulats J, Vilaro S. Alpha v integrin antagonists induce the disassembly of focal contacts in melanoma cells. *Eur J Cell Biol*. 2000 Jul;79(7):502-12.
- Piulats J, Mitjans F. "Angiogenic switch pathways" in *Principles of Molecular Oncology*, 2000, 269-291.
- Eds: Bronchud, Foote, Peters, Robinson editors. Humana Press, New York.

- Miljans F, Meyer T, Fittschen C, Goodman S, Jonczyk A, Marshall JF, Reyes G, Piulats J.  
In vivo therapy of malignant melanoma by means of antagonists of alphav integrins.  
*Int J Cancer.* 2000 Sep 1;87(5):716-23.
- Petitclerc E, Stromblad S, von Schalscha TL, Miljans F, Piulats J, Montgomery AM, Cheresh DA, Brooks PC.  
Integrin alpha(v)beta3 promotes M21 melanoma growth in human skin by regulating tumor cell survival.  
*Cancer Res.* 1999 Jun 1;59(11):2724-30.

#### POSTERS

- Fernandez Y, Queralt J, Pavia X, Piera C, Ramirez de Arellano I, Miljans F, Messeguer R, Piulats J, Carrió I. Multitracer *in vivo* assessment of tumor models with 18F-fluorothymidine, 18F-FDG and N-ammonia PET in mice. EANM'06. Annual Congress of the European Association of Nuclear Medicine (EANM). Athens, 30 september-4 October 2006
- Fernandez Y, Queralt J, Pavia X, Ramirez de Arellano I, Miljans F, Piulats J, Carrió I. Visualización de la actividad proliferativa tumoral mediante 18F-fluorotimidina en glioma y melanoma en ratón. XXVII congreso nacional de la sociedad española de medicina nuclear (SEMN). Granada, 7-9 junio 2006
- T Cupido, J Ruiz-Rodríguez, J Adan, F Miljans, R Messeguer, J Spengler and F Albericio. Tuning of Intramolecular H-bonds on Cyclopeptides by Ester Scan Synthesis, Conformation and Biology of RGD Depsipeptides. 20th American Peptide Society Symposium. June 26 – 30, 2007, Montréal, Quebec, Canada
- Eloi Montañez, Roser Pagan, Ricardo P Casaroli, Manuel Reina, Francesc Miljans, Jaume Piulats and Sener Vilaró. Alpha-v-integrin antagonists promote tube regression of hevec cells in different *in vitro* angiogenesis assays. 43rd ETCS Congress. Granada, Spain (2001).
- Eloi Montañez, Roser Pagan, Ricardo P.Casaroli-Marano, Manuel Reina, Francesc Miljans, Jaume Piulats and Sener Vilaró. Alpha-v-integrin antagonists promote tube regression in angiogenesis assays *in vitro*. Tumor Angiogenesis Special American Association Cancer Research Meeting. Traverse City, USA (2000).

#### ANNEXES

#### STAYS IN OTHER CENTERS

- 1997 The SCRIPPS Research Institute, Department of Vascular Biology, La Jolla, San Diego, California, USA.  
PROJECT: "Integrins in tumor angiogenesis"
- 1990 Centre National de la Recherche Scientifique. Institut de Recherches sur le Cancer. Hospital Paul Brousse, Department of Immunochemistry, Villejuif, France.  
PROJECT: "FAP protein, a new pancreatic tumor marker"